Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 2, 27-41, 43-47, 49, 50, 52-55, 60, 61, 78-80, 82-93, and 96 are pending in the application, with 1, 46, 49, and 52 being the independent claims. Claims 56-59, 62-77, 81, 94, and 95 are sought to be canceled without prejudice to or disclaimer of the subject matter therein solely to expedite prosecution. Support for the amendments to claims 1, 46, 49, and 52 is found in the claims as originally filed. Claims 78, 82, 84, 85, and 87 have been amended to match the amendment to claim 52. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 1, 2, 27-41, 43-47, 49, 50, 52, 53, 63-65, 69-93, 95, and 96 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for gossypol compounds that have aldehyde groups and isopropyl groups, allegedly does not reasonably provide enablement for apogossypol and Schiff's base derivatives of gossypol that do not have an aldehyde group on the gossypol compounds. (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that Shelley *et al.* (Anticancer Drugs, 11:209 (2000)) teach that apogossypol and Schiff's base derivatives of gossypol are inactive against tumor cell lines, due to the fact that the aldehyde groups are missing. (Office Action, page 2). The Examiner also alleges that Shelly *et al.* teach that the ethyl derivatives of gossypol show negligible inhibitory activity. (Office Action, page 3).

Applicants respectfully disagree. Present claims 1, 2, 27-41, 43-47, 49, and 50 do not encompass Schiff's base derivatives of gossypol as independent claims 1, 46, and 49 indicate that the gossypol compound is selected from the group consisting of (±)-ethyl gossypol, (-)-ethyl gossypol, (+)-ethyl gossypol, (±)-apogossypol, (-)-apogossypol, (+)-apogossypol, (±)-apogossypol acetic acid, (-)-apogossypol acetic acid, (+)-apogossypol acetic acid, (±)-ethyl apogossypol, (-)-ethyl apogossypol, and (+)-ethyl apogossypol. None of these compounds are Schiff's base derivatives of gossypol.

Shelley *et al.* is incorrect regarding the anticancer activity of apogossypol. Becattini *et al., Chem. Biol. 11*:389 (2004) teach that apogossypol is capable of binding and inhibiting Bcl-2 and Bcl-X_L with high affinity and induces apoptosis of tumor cell lines. Thus, the claimed use of apogossypol and apogossypol derivatives is enabled.

The Examiner further alleges that Shelley *et al.* disclose that the ethyl derivatives of gossypol show negligible inhibitory activity to tumor cell lines similar to that of Schiff's base derivatives. (Office Action, page 3). This is an incorrect interpretation of Shelley *et al.* The passage at p. 214, col. 2, paragraph 2 refers to studies disclosed in reference 27 (Liang *et al., Invest. New Drugs 13*:181 (1995)) on Schiff's bases of gossypol, including the ethylamine

Schiff's base. The referenced studies suggest that the isopropylamine Schiff's base of gossypol is the only Schiff's base derivative that has anticancer activity. The paragraph does not discuss ethylgossypol derivatives as is presently claimed.

Independent claim 52 as amended does not encompass the use of apogossypol or Schiff's base derivatives of gossypol as the claim is directed to the use of a gossypol compound selected from (±)-gossypol, (-)-gossypol, (±)-gossypol acetic acid , and (-)-gossypol acetic acid. Thus, the rejection is moot for claim 52 and all claims dependent therefrom.

The Examiner's concern regarding the anticancer activity of Schiff's base derivatives of gossypol is irrelevant to the present claims. The Examiner's reliance on Shelly *et al.* to allege the lack of enablement for apogossypol is misplaced as the art has shown that apogossypol has anticancer activity. It is respectfully requested that the rejection of claims 1, 2, 27-41, 43-47, 49, 50, 52, 53, 63-65, 69-93, 95, and 96 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 52-62 and 78-96 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Flack *et al.* (U.S. Patent No. 6,114,397) in view of Merck Manual of Diagnosis and Therapy. (Office Action, page 4). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [i]t would have been obvious to one of ordinary skill in the art at the time of invention to employ both radiation and gossypol compounds of '397, as racemic or pure enantiomers, in a method and composition of treating cancer. It would have been obvious to one of ordinary skill in the art at the time of invention to optimize

> the therapeutic regimen of the cancer treatment employing the gossypol compounds and radiation.

(Office Action, page 5). The Examiner further acknowledges the unexpected synergistic benefits demonstrated in the present specification but alleges that the unexpected results are not commensurate with the scope of the subject matter claimed. (Office Action, pages 8-9).

Applicants respectfully disagree. Claims 56-59, 62, 81, 94, and 95 have been canceled solely to expedite prosecution, rendering that portion of the rejection moot. Claim 52 as amended is directed to methods of treating or ameliorating cancer comprising administering a gossypol compound selected from racemic or (-)-gossypol or racemic or (-)-gossypol acetic acid and one or more second agent(s) selected from docetaxel, paclitaxel, and/or radiation, wherein the combination of a gossypol compound and a second agent produces a synergistic effect with respect to one or more of tumor shrinkage, tumor loss, time to tumor progression, or survival. Flack *et al.* do not disclose any examples of combination treatment with gossypol and docetaxel, paclitaxel, and/or radiation, and therefore do not show a synergistic response to combination treatment with respect to one or more of tumor shrinkage, tumor loss, time to tumor progression, or survival. One of ordinary skill in the art reading Flack *et al.* would not have a reasonable expectation that the particular claimed combinations of gossypol compounds with the specified anticancer agents or radiation produce a synergistic effect with respect to the specified outcomes. Thus, there can be no *prima facie* case of obviousness of claim 52 and dependent claims 53-55, 60, 61, 78-80, 82-93, and 96 over the cited art.

In contrast, the present specification discloses the synergistic effects of combinations of gossypol compounds with docetaxel, paclitaxel, and radiation in treating or ameliorating cancer.

See, *e.g.*, Examples 12, 16, 18, 19, 20, and 22 and Tables 8-11, 14, and 15. (-)-Gossypol shows clear synergistic effects with multiple anticancer agents. Racemic gossypol is less potent than (-)-gossypol but still provides a synergistic effect when combined with anticancer agents (see Fig. 19). Gossypol acetic acid is a composition containing gossypol with acetic acid as a solvate and is known in the art to exhibit the same activity as gossypol. The claims as amended are commensurate in scope with the unexpected synergistic results shown in the specification. Therefore, any alleged *prima facie* case of obviousness is overcome by this showing.

It is respectfully requested that the rejection of claims 52-62 and 78-96 under 35 U.S.C. § 103(a) be withdrawn.

Claims 1, 2, 27-41, 43-47, 49, 50, 52-62, 66-68, and 78-96 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Shelley *et al.* in view of Flack *et al.* (U.S. Patent No. 6,114,397) and Merck Manual of Diagnosis and Therapy. (Office Action, page 6). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that it would have been obvious to employ hemigossypolone in a method of treating a tumor based on the teaching of Shelley *et al.* and Flack *et al.* of the anticancer activity of gossypolone. (Office Action, page 7).

Applicants respectfully disagree. Claims 56-59, 62, 66-68, 81, 94, and 95 have been canceled solely to expedite prosecution, rendering that portion of the rejection moot. Independent claims 1, 46, 49, and 52 as amended are not drawn to the use of hemigossypolone for the treatment of hyperproliferative diseases. Thus, the rejection has been rendered moot.

It is respectfully requested that the rejection of claims 1, 2, 27-41, 43-47, 49, 50, 52-62, 66-68, and 78-96 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

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